Prenatal exposure estimation of BPA and DEHP using integrated external and internal dosimetry: A case study

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ABSTRACT

Exposure to Endocrine disruptors (EDs), such as Bisphenol A (BPA) and di (2-ethylhexyl) phthalate (DEHP), has been associated with obesity and diabetes diseases in childhood, as well as reproductive, behavioral and neurodevelopment problems. The aim of this study was to estimate the prenatal exposure to BPA and DEHP through food consumption for pregnant women living in Tarragona County (Spain). Probabilistic calculations of prenatal exposure were estimated by integrated external and internal dosimetry modelling, physiologically based pharmacokinetic (PBPK) model, using a Monte-Carlo simulation. Physical characteristic data from the cohort, along with food intake information from the questionnaires (concentrations of BPA and DEHP in different food categories and the range of the different food ratios), were used to estimate the value of the total dietary intake for the Tarragona pregnancy cohort. The major contributors to the total dietary intake of BPA were canned fruits and vegetables, followed by canned meat and meat products. In turn, milk and dairy products, followed by ready to eat food (including canned dinners), were the most important contributors to the total dietary intake of DEHP. Despite the dietary variations among the participants, the intakes of both chemicals were considerably lower than their respective current tolerable daily intake (TDI) values established by the European Food Safety Authority (EFSA). Internal dosimetry estimates suggest that the plasma concentrations of free BPA and the most important DEHP metabolite, mono (2-ethylhexyl) phthalate (MEHP), in pregnant women were characterized by transient peaks (associated with meals) and short half-lives (<2 h). In contrast, fetal exposure was characterized by a low and sustained basal BPA and MEHP concentration due to a lack of metabolic activity in the fetus. Therefore, EDs may have a greater effect on developing organs in young children or in the unborn child.

Keywords: Endocrine disruptors; Bisphenol A (BPA); di (2-ethylhexyl) phthalate (DEHP); mono (2-ethylhexyl) phthalate (MEHP); physiologically based pharmacokinetic (PBPK) model; Prenatal exposure.

1. Introduction

The endocrine system secretes hormones which regulate the metabolic functions of the body. Endocrine disruptors (EDs) are substances that can mimic or partly mimic naturally occurring hormones in the body like estrogens, androgens, and thyroid hormones (Matsui, 2008). EDs can also bind to a receptor within a cell and block the endogenous hormone from binding. (Sharma et al., 2016 a). Therefore, EDs can interfere or block the way natural hormones or their receptors are made or controlled (Thomson and Grounds, 2005). Bisphenol A (BPA) and di (2-ethylhexyl) phthalate (DEHP), among others, are very important EDs due to the widespread distribution of products that contain them. According to the World Health Organization (WHO), both of these chemicals can cause adverse health effects in an intact organism, or its progeny (Hughes et al., 2006; Meeker, 2012; WHO, 2012). The effects of prenatal and early exposures to EDs may be manifested any time in life (Giulivo et al., 2016; Sharma et al., 2016 a).

Around 3 billion kilograms of BPA are produced annually worldwide and over 100,000 kilograms of this compound are released annually into the atmosphere (Myridakis et al., 2016). BPA is used in industry for the production of resins and polycarbonate plastic. Although the use of BPA in Europe is banned for the manufacture of plastic materials in contact with food intended for children (0-3 years) (European-Parliament, 2011), it is not banned in polycarbonate (PC) plastics for other uses. It can be found in food and beverage processing, and in many other commercial products such as epoxy resin cans, dental sealants, personal care products, baby bottles, building materials, flame retardant materials, optical lenses, materials for the protection of window glazing, DVDs, and household electronics (Geens et al., 2012; Myridakis et al., 2016). Although the ingestion of BPA from food or water is the predominant route of exposure (Lorber et al., 2015), there are other nonfood routes, such as inhalation of free BPA (concentrations in indoor and outdoor air), indirect ingestion (dust, soil, and toys), and dermal route (contact with thermal papers and application of dental treatment), which contributes to the total BPA exposure (Myridakis et al., 2016). In addition, recent studies (De Coensel et al., 2009; Sungur et al., 2014) have seen that temperature has a major impact on the BPA migration level into water; an increase from 40 ºC to 60 ºC can lead to a 6 - 10 fold increase in the migration

level (De Coensel et al., 2009). The TDI of BPA is 4 µg/kg bw/day (EFSA, 2015). However, other studies have demonstrated that dosages below the current TDI could cause significant effects in animal models (Rezg et al., 2014). In the context of developmental risk, some authors affirm that BPA can affect the reproductive system and adipocyte differentiation (Myridakis et al., 2016). Especially for children, exposure to these EDs appears to be related to altered birth weight, male genital abnormalities, and behavioral and neurodevelopmental problems (Rochester, 2013; Tewar et al., 2016).

Phthalates are ubiquitous environmental contaminants made up of dialkylesters or alkyl and aryl esters oforthophthalic acid (1,2-dicarboxylic acid). High-molecular-weight phthalates (HMWP) can be found in tubing, vinyl flooring, and wall covering (Mallozzi et al., 2016). Low-molecular-weight phthalates (LMWP) more commonly can be present in personal care products (shampoo, cosmetics, fragrances and nail polish) (Mallozzi et al., 2016). Phthalates are also found as both inert and active ingredients in some pesticide formulations (EFSA, 2015). It is known that food is the major source of exposure to diisobutyl (DiBP), di-n-butyl (DnBP), and di (2-ethylhexyl) (DEHP) phthalate (Wormuth et al., 2006). However, other sources such as dermal contact with products that contain them, dust ingestion and inhalation, are also potential contributors to human exposure (Arbuckle et al., 2016). An additional exposure route for young children is through mouthing toys, childcare articles and other products containing phthalates. Through mouthing of these products, phthalates can dissolve in saliva and finally be absorbed into the bloodstream. (De Coensel et al., 2009). Once absorbed, phthalate diesters are quickly metabolized into monoesters (as MEHP), which are biologically active and ultimately excreted in urine (Genuis et al., 2012). DEHP metabolite, the mono (2-ethylhexyl) phthalate (MEHP), is the most toxic and active one among these phthalates (Gobas et al., 2016). The EFSA and the European Chemical agency (ECHA) established a TDI of 50 µg/kg bw/day for DEHP (EFSA, 2015; ECHA, 2010). In the context of risk, DEHP and its metabolite MEHP, mainly affect estrogen production and action in granulosa cells, resulting in hypo-estrogenic, polycystic ovary and anovulatory cycles. This leads to infertility and affects the reproductive development of the fetus (Das et al., 2014; Davis et al., 1994; Lovekamp-Swan and Davis, 2003; Wang et al., 2015).

BPA and phthalates are considered “non-persistent” EDs because they are rapidly eliminated from the human body. Despite their short biological half-lives, exposure is prevalent and continuous because of their widespread use in food and everyday products, leading to consistent detection of these EDs in human biological matrices like urine and blood. BPA undergoes glucuronidation and sulfation producing BPAG and BPAS in the liver, respectively (Hanioka et al., 2008; Kim et al., 2003). These metabolites are not toxic in comparison to BPA (Gramec Skledar and Peterlin Mašič, 2016). Instead, DEHP is metabolized into mono (2-ethylhexyl) phthalate (MEHP), which is more toxic than DEHP (Gobas et al., 2016; Latini, 2005).

Optimal development and health in early life are key factors for health and wellbeing during later childhood and adulthood. It has been hypothesized that adult health and disease have their origin in the prenatal and early postnatal environment, a concept referred to as the Developmental Origins of Health and Disease (Hanson and Gluckman, 2011). There are various parameters early in life, which are indicators for development later in life. The exposition to these EDs in the early period of life conditions to suffer and develop illnesses like obesity and type 2 diabetes in childhood and adulthood (Casas et al., 2011; De Cock et al., 2014; Myridakis et al., 2016).

The aim of this study is to estimate the prenatal exposure to EDs (BPA and DEHP) through the dietary intake of pregnant women using integrated external and internal dosimetry estimation. To assess the prenatal exposure, we used a mathematical physiologically based pharmacokinetic model (PBPK) adapted for pregnancy, in order to know the internal dosimetry levels of EDs in the fetus. PBPK models are mathematical representations of the human body aimed at describing the time course distribution of chemicals in human tissues (Fàbrega et al., 2016). In recent years, PBPK models have been used in human health risk assessment to estimate the burdens of chemicals in human tissues, thus avoiding the analysis of this kind of samples (Fàbrega et al., 2014; Fàbrega et al., 2015; Schuhmacher et al., 2014). The present study is in the framework of the “HEALS” project (FP7-603946), Health and environmental-wide associations based on large population surveys.

2. Materials and Methods

2.1 Study Population cohort

The study population comprises a cohort of pregnant women and ongoing birth cohort. The pregnant women were recruited during the first trimester of pregnancy as part of the European "HEALS" project. The recruitment of pregnant mothers has started in March 2016 and in the present study 45 mother-child pairs were included. Women were informed of the study during their first prenatal visit to the University Hospital "Sant Joan de Reus", in Reus, Catalonia, Spain. Women were eligible to participate according to the following inclusion criteria: ≥16 years, intention to deliver at the reference hospital, and no problems with the communication language. This study was approved by the Ethical Committee of Clinical Research of the University Hospital "Sant Joan de Reus". Written informed consent was obtained from the participants.

2.2 Pregnancy and diet

Diet has been considered the primary source of BPA and phthalates exposure (Lakind and Naiman, 2010; Maffini et al., 2006; Welshons et al., 2006). Therefore, face-to-face food frequency questionnaires (FFQ) and personal interviews were used in order to determine the pregnant women's dietary intake of BPA and DEHP, like other authors had done it before (Casas et al., 2011; Myridakis et al., 2016). Apart from food frequency questions, the questionnaires also included a set of questions targeting to know other sources of these compounds.

Dietary factors were assessed using FFQ (times per week), the questionnaires give information about general food intakes by mothers during pregnancy trimesters. These questionnaires were originally designed to assess average dietary intakes during two phases of pregnancy: the 1st FFQ covered the year before pregnancy and the 2nd FFQ covered the whole pregnancy including the last period until birth. Intake frequency for each food item was

converted to an average daily intake for each participant and then expressed like servings/week. Different food items from the FFQs administered during pregnancy study were classified in 8 general food groups: a) Grains and grain-based products (cereals, pasta, and bread), b) Milk and dairy products (milk, yogurt, hard cheese and fresh cheese), c) Meat and meat products (chicken, turkey, beef, pork, lamb and minced meat), d) Fish and other seafood (white fish, blue fish and seafood), e) Fruits and vegetables (salad, green beans, swiss chard, spinach, garnish vegetables, potatoes, and), f) Legumes (lentils, chickpeas, and white beans), g) Ready to eat (pre-cooked and canned food) and h) Water. In addition, questions potentially relevant to EDs exposure were asked: type and frequency of water consumption (bottled water or tap water), organic food consumption, heating and use of plastic microwave food containers and consumption of plastic packaged food or canned food. Especially canned food is considered as the predominant source of BPA and DEHP (Hartle et al., 2016; Schecter et al., 2013).

Face-to-face interviews were conducted with mothers during pregnancy about habits and lifestyle, in order to know relevant information related to the exposure to EDs, such us smoking or alcohol drinking, hobbies or activities that they usually do, place of living and work environment.

2.3 BPA and DEHP total dietary intake assessment

The estimation of the total dietary intake of BPA and DEHP for pregnant women was calculated according to equation A.1.

$$\text{Total dietary intake} = (C_{BPA/DEHP} \cdot F_r \cdot F_f) / BW / 7 \qquad \text{Eq. (A.1)}$$

Where $C_{BPA/DEHP}$ is the BPA or DEHP concentration found in the different food categories (in μg/kg); F_r is the food ingestion ration (in kg/ration); F_f is the food frequency consumption (in ration/week), and BW is the body weight (in kg). The total dietary intake is given in μg/kg bw/day. Data used to assess the total dietary intake of BPA and DEHP is shown in Table 1.

Concentrations of BPA and DEHP in the different food categories were taken from the literature with a preference rule of Spanish > Mediterranean > European average > other available data. The range of the different food rations was taken from Spanish Society of Community Nutrition (Serra Majem, 2011). Finally, the food frequency and body weight were taken from the cohort of the present study. To deal with variability and uncertainty of parameters mentioned, probabilistic estimation of the total dietary intake was performed using Monte-Carlo simulation. Monte-Carlo simulation is a common approach used to incorporate variability and uncertainty of the parameters mentioned into the estimation of human health exposure (Mari et al., 2009; May et al., 2002; Rovira et al., 2016; Schuhmacher et al., 2001). Table 1 includes the probabilistic distribution of parameters for the calculation of human health exposure. In this study, Monte-Carlo simulation was carried out by Oracle Crystal Ball©. This program is able to calculate risk based on the propagation variable of variability and uncertainty given by each parameter probability function until a certain number of iterations. An iteration size of 100,000 was used. Appropriate probabilistic distributions were used according to the input parameters (concentrations of BPA and DEHP in the different food categories, food fraction, food frequency, and body weight): Log-normal, triangular and uniform distribution (Table 1). In general, we used triangular distribution when the literature data was limited; in these cases, the minimum, maximum and mean values of the parameter were considered. We used log-normal distributions only for positive values and when literature data was available (mean and standard values). Finally, we used the uniform distribution when the information available was only the min-max range assuming equal probability of occurrence. To simulate different exposure scenarios, detailed data from the cohort study (food frequency and the body weight of the mothers) has also been considered. A complementary aspect of the Monte-Carlo study is the possibility of creating sensitivity charts, which show information about how much each predictor variable (each food item) contributes to the uncertainty or variability of prediction (Shade and Jayjock, 1997).

2.4 Cohort Characteristics

A description of the characteristics of the study population is shown in Table 2. 43 % of mothers had university studies and 25 % had more than 12 years of education. Almost 75 % of the mothers were between 30 and 39 years old and 15 % were actively smoking during pregnancy. Regarding water consumption, most of the mothers drink bottled water (70 %) and most of them never eat organic products (56 %). Almost 50% of our cohort eats fast-food once a week and 70 % of them eat canned food between 1 and 3 times per week. This data can be directly related to the cohort's complexion (around 50 % of the pregnant mothers were overweight, and 15 % of them were obese).

2.5 Tissue dosimetry model (PBPK)

A previously developed and validated adult PBPK model of BPA (Sharma et al., 2016 b, unpublished) and of DEHP (Sharma et al., 2016 c, unpublished) was adapted for the pregnancy-PBPK model and was used to estimate internal dosimetry of mothers and fetuses for the present cohort study. The basic structure of adult human PBPK model (which included plasma, liver, kidneys, filtrate, fat, brain, gonads and a rest of the body compartment for the remaining tissues) (Figure 1), has been adapted for pregnant women model. In addition, compartments of placenta and fetus were considered as a sub-model in order to predict the internal dosimetry for the fetus. It was subcategorized again into liver, brain, and plasma (Figure 1). The physiological and chemical-specific parameters were adapted from the adult human model and modified for the fetuses and mothers as a function of the gestational period. The metabolism capacity in the fetus was scaled from the adult data. The source of exposure to fetuses was through free fraction of chemicals into mothers placenta, considering that fetuses exposure is directly related to mother's exposure. The placental-fetal unit assumes a bidirectional transfer process describing chemical transfer between mother's placenta to fetus plasma and fetus plasma to the mother. A detailed description of standard and pregnancy specific model equations are provided in supplementary material (Annex-I). All physiological parameters were considered as a function

of gestational day and model equations were adapted from different literature sources and are provided in Annex-I. Metabolic kinetic parameters namely Vmax (maximum rate of reaction) and Km (affinity of the substrate for the enzyme), for mothers and fetuses, were taken from in-vitro studies and were scaled to in-vivo. The chemical-specific parameters are also provided in supplementary material (Annex-I).

PBPK model inputs were the outputs of the Monte-Carlo simulation used previously for the exposure assessment. We considered three total dietary intake scenarios of BPA and DEHP: 5th percentile, mean and 95th percentile. In addition, a biologically active metabolite of DEHP, MEHP was considered as relevant internal exposure chemical and was used as an input in the PBPK simulation model to estimate fetus exposure. DEHP is rapidly metabolized into MEHP (Latini, 2005) and normally stay in the systemic circulation of mother's body and pass to the fetuses.

3. Results and Discussion

3.1 BPA and DEHP total dietary intake and food categories contribution

The contribution of each food item to the total dietary intake for the Tarragona population cohort was assessed in a probabilistic way using a Monte-Carlo simulation. Figure 2, summarizes the food categories contributing to the total dietary intake of BPA (Figure 2, A.1) and DEHP (Figure 2, A.2)

Regarding BPA (Figure 2, A.1), the total dietary intake mean value was 0.72 μg/kg bw/day (0.28 and 1.42 μg/kg bw/day for 5th and 95th percentile, respectively). The variable showing the greatest contribution to the total dietary intake mean value was "fruits and vegetables" with 49 %, followed by "meat and meat products" with 26 %. The contribution of the remaining food categories were 8 %, 5 %, 4 %, 4 %, 2 % and 2 % corresponding to "fish and other seafood", "water consumption" (bottled water and tap water were considered, but only bottled water added risk of exposure to BPA), "grain and grain-base products", "milk and dairy products", "ready to eat (including canned food)" and "legumes", respectively.

The high contribution (49 %) of "fruits and vegetables" to the total dietary intake was due to the high consumption of this food item (an average of 21.1 servings per week), typical of a Mediterranean diet. The concentration of BPA in fruits and vegetables was not excessively high compared with other food items, with an average concentration of 9.92 μg/kg, although there was a maximum value of 116 μg/kg due to canned fruits and vegetables. It should be noted that fruits and vegetables are also packaged in plastic and in these cases, migration of BPA to the products occurs (Lakind and Naiman, 2010). The next major contributor to the total dietary intake was "meat and meat products" with a contribution of 26 % and an average concentration of BPA of 36.9 μg/kg and a maximum value of 395 μg/kg (canned). In this case, unlike the group of fruits and vegetables, although the frequency of consumption is lower, the levels of BPA in this category are higher.

EFSA (2015) published its comprehensive re-evaluation of BPA exposure and toxicity, in January 2015 it established a TDI of 4 μg/kg bw/day for BPA. In the present study, although the maximum value estimated was 4.40 μg/kg bw/day, 95% of the population were under 1.41 μg/kg bw/day. In addition, the present study data matches with the established values, which FAO (Food and Agriculture Organization)/WHO set during the last expert meeting in order to review the toxicological and health aspects of BPA. For adults, the highest exposure estimates did not exceed 1.4 μg/kg bw per day at the mean and 4.2 μg/kg bw/day at the 95th percentile (FAO/WHO, 2010).

Regarding DEHP, the total dietary intake mean value for our cohort was 1.00 μg/kg bw/day (0.41 μg/kg bw/day and 2.01 μg/kg bw/day for 5th and 95th percentile, respectively) (Figure 2, A.2). The maximum contribution to this exposure comes from "milk and dairy products" with 56 %, followed by "ready to eat (including canned food)" with 30 %. The other food items "grain and grain-base products", "meat and meat products", "fruits and vegetables", "fish and other seafood" and "water consumption" (bottled water and tap water were considered) contributed to 6 %, 4 %, 3 %, 1 %, and 1 %, respectively.

On the one hand, the high contribution (56 %) of "milk and dairy products" category to the total dietary intake of DEHP in the present study is due to the high DEHP levels in milk and

dairy products (with a mean and maximum of 126 and 173 µg/kg, respectively) in comparison to other categories. DEHP contamination of milk and dairy products occurs in several stages: contaminated DEHP feed, mechanical milking process, and migration from packaging material used in milk and dairy products (Fierens et al., 2013). Milk and dairy products were the second most consumed food item during pregnancy (an average of 6.86 servings per week), which can also be related to the general recommendation for a pregnant woman of maintaining optimal levels of calcium in the body in order to prevent adverse gestational outcomes (WHO, 2013). Also, the high concentration of DEHP in this food group is due to lipophilic nature of phthalates; and for this reason, it is assumed that high-fat foods contain more phthalates than low-fat food products (Fierens et al., 2013). Various authors (Page and Lacroix, 1989; Sharman et al., 1994) reported that there is a positive relationship between the fat content of a dairy product and the DEHP content in that product. The second most contributed food item to the total dietary intake of DEHP was ready to eat food (30 %). It has been found a strong correlation between fast food intake and phthalates exposure but not with BPA exposure. This evidence coincides with another study from the USA, in which they observe the same evidence of a positive dose-response relationship between fast food intake and DEHP exposure but not for BPA (Zota et al., 2016).

The EFSA and the ECHA established the total daily intake for DEHP to 50 µg/kg bw/day (EFSA, 2015; ECHA, 2010). In this study, both, the maximum (11.4 µg/kg bw/day) and the 95th percentile (2.01 µg/kg bw/day) were far below this threshold.

Finally, the concentration of BPA and DEHP in bottle water was found in the literature data. However, in tap water, only levels of DEHP was found (Table 1). The presence of DEHP in tap water is due to leaching from PVC tubes and others materials from the pipes (Santana et al., 2014).

3.2 Dietary exposure compared to other countries

Table 3 shows the BPA and DEHP total dietary intake in adult populations in different countries. All data from the studies in Table 3 were experimentally analyzed in different food items.

Regarding BPA, it can be observed that the mean daily intake of it in the Tarragona cohort (Spain) was in the same order of magnitude as data presented for the Spanish cohort in EFSA report (EFSA b) (EFSA, 2013) and it was slightly below the European mean dietary intake of previous EFSA report (EFSA, 2006). Total dietary intake of BPA in Tarragona was also in the same order of magnitude as in Taiwan (Chen et al., 2016). However, data from countries such as France (Bemrah et al., 2014), Belgium (Geens et al., 2010), and USA (Lorber et al., 2015) were one order of magnitude lower; whereas, countries such as New Zealand (Thomson and Grounds, 2005), and Norway (Sakhi et al., 2014) were two orders of magnitude lower than the Tarragona study.

Regarding DEHP, it can be observed that the mean daily intake in the Tarragona cohort (Spain) was in the same order of magnitude as data presented from other European studies such as Belgium (Sioen et al., 2012), France (Martine et al., 2013) and Switzerland (Dickson-Spillmann et al., 2009). The present study estimations were in the same order of magnitude as Norway (Sakhi et al., 2014), USA (Schecter et al., 2013), Germany (Fromme et al., 2007) and China (Sui et al., 2014). However, DEHP exposure in countries like Cambodia (Cheng et al., 2013) and Germany (Heinemeyer et al., 2013) were presented one order of magnitude higher than the Tarragona's results.

It should be noted that dietary preference and food sources in different regions might lead to variability of the estimated daily intakes of EDs. In addition, it is important to mention that not all studies have considered exactly the same items and that could lead to differences in results. Despite this, estimated daily dietary exposure to DEHP and BPA in our study is comparable with other studies worldwide (Table 3).

3.3 Internal dosimetry

The chemicals' dose inputs considered to run the PBPK, were probabilistically estimated by Monte-Carlo simulation (section 3.1). From probabilistic distribution, three total dietary intake reference scenarios were selected for BPA and DEHP: the 5th percentile, the mean and the 95th percentile. The outputs generated after running the model were selected considering the metabolites generated, their toxicity, gestational period and ability to reach the fetus. For this reason, only free BPA and MEHP (a metabolite of DEHP) were considered.

The simulation was performed for pregnant women and fetus for 24 hours during the 24th gestational week. This period was selected because at this time fetus organs are more developed and able to incorporate right biological process. This helps us to explain the difference in metabolic processes in mothers and fetuses. Normally, at the early stage of pregnancy, for both BPA and MEHP, fetus plasma concentration level is higher due to low or no metabolic activities in the fetus (Gauderat et al., 2016; Latini et al., 2003). In order to understand the elimination profile of the chemicals (BPA and MEHP) in the body, single dose simulation for all three exposure scenarios (5th percentile; mean; 95th percentile) was simulated. Time versus plasma concentration (for mothers and fetuses) of BPA and MEHP are shown in Figure 3 and 4, respectively. Due to the fast absorption properties of BPA and DEHP, simulated concentration curves show a sharp peak concentration observed within 1 hour of intake. Both, BPA and MEHP are fast elimination chemicals, with a half-life of fewer than 2 hours and complete elimination within 24 hours in adult (mother). The elimination of BPA and MEHP in the fetuses is slower than mothers as the fetal metabolic activity is lower comparing mother's metabolism. In general, it was observed that BPA and MEHP stay longer in the fetal body, which may cause higher risk to fetuses compare with the mothers even for lower exposure scenario (Figure 3 and 4). Similar results have been observed by Sharma et al., (2016 b, c, unpublished) for BPA and MEHP, respectively. In reality, the oral exposure has multiple intakes and in that case, the residence time of the chemical in the human body increases. However, absorption and elimination profile of chemical after three intakes have little or no effect. Figure 5 summarizes the levels concentration of BPA in plasma in mothers and fetuses considering three oral intakes.

To simulate three doses scenario, the single intake was divided into three with 8 hours of interval. The area under the curve for each day has increased significantly with higher residence time but lower peak compares to one oral dose scenario. In multiple dose scenarios, absorption peak concentration for each intake time and the half-life of elimination are similar to single dose scenario with 1 hour for the peak and less than 2 hours for the half-life. However, in multiple dose scenarios, as each intake is lower than single-dose intake, peak concentrations for the corresponding intake are lower. For example, the peak concentration of BPA (95^{th} percentile) for mothers and fetuses considering only one dose were 0.047 µg/L and 0.039 µg/L, respectively and considering multiple doses, were 0.015 µg/L (95^{th} percentile) and 0.018 µg/L (95^{th} percentile) for mothers and fetuses, respectively; this peaks concentrations were around 1/3 of the value for one dose. Although, in the case of fetus, the peak concentration was slightly more than 1/3 due to his low metabolic capacity. In the case of MEHP, the profile was the same as the BPA. For only one dose the plasma concentration peak was 11 µg/L (P95) in the mothers and 9 µg/L (P95) in the fetuses and considering three doses, it was obtained values that were the third part of the previous ones mentioned. It was observed that the concentration peaks of DEHP in plasma were higher compared with BPA. However, it should be noted that the probabilistic total dietary intake of DEHP obtained by Monte-Carlo was higher than the total dietary intake obtained for BPA.

Despite their short biological half-lives, exposure is prevalent and detectable in blood matrix at any time. Mothers are able to decrease much more the basal levels of these chemicals compared to the fetuses due to her metabolic activity. For that reason, fetuses are always subject to a risk of constant exposure. The results of the present study were not comparable with biomonitoring studies for multiple reasons. Firstly, in the present case study, only oral exposure was estimated whereas, in reality, both BPA and DEHP have multi-route exposure with significant contribution from coming from dermal exposure (Myridakis et al., 2016). Secondly, both BPA and DEHP show high variability in their internal dosimetry with no steady state concentration, which makes the timing of biomonitoring sampling very relevant. Which means, the concentration levels of the EDs obtained from plasma are subject to different conditions such as

the diet of each patient, the time of sampling (it will not be the same concentration if it is collected after longer period without any exposure or closer to peak hour of exposure) and the routes of exposure (oral vs dermal).

4. Conclusions

The aim of this study was to estimate the prenatal exposure to EDs (BPA and DEHP) through the dietary intake of pregnant women using the interview-based method, in order to improve the knowledge about the risks that they pose to prenatal health. To assess the early exposure, integrated external and internal dosimetry estimate was performed.

Canned fruits and vegetables followed by canned meat and meat products were the major contributors to the dietary exposure to BPA in pregnant women population in Tarragona (Spain). For DEHP, milk and dairy products followed by ready to eat food (included canned dinners) were the most important contributors to the estimated dietary exposure. In spite of dietary variation and resulting differences in exposure, the total dietary intake estimate for BPA and DEHP was considerably lower than their respective current TDI values established by EFSA (4 and 50 μg/kg bw/day, respectively) (EFSA, 2015). Internal dosimetry simulations carried out in this study suggest that free BPA and MEHP plasma concentrations in women were characterized by transient peaks (associated with meals). In contrast, fetal exposure was characterized by a low but sustained basal BPA and MEHP concentration due to a lack of metabolic activity in the fetus.

The ongoing research is to validate the PBPK model with biological samples from this cohort and demonstrate that this methodology allows the determination of BPA and MEHP for monitoring in plasma and urine biological matrices and the PBPK model can predict the prenatal exposure of the child/fetus to EDs.

Finally, the health implications of this fetal exposure to BPA and MEHP should be addressed because they are associated with infertility issues and reproductive development of

the fetus. Therefore, a strategy to reduce their exposure is to regulate their production and restrict their use in articles specially meant for childcare and pregnant women.

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Table 1. Monte-Carlo parameter description to assess the total dietary intake of BPA and DEHPX

Parameter	**Symbol**	**Units**	**Type**	**Distribution** [a]	**Reference**
BPA concentration in [b]					
	C_{BPA}	–	–	–	–
Grains and grain-based products		–	μg/kg	T	18.0(0-47.5) EFSA, 2015
Fruits and vegetables		–	μg/kg	T	9.93 (0-116) EFSA, 2015
Legumes		–	μg/kg	T	51.5 (0-103) EFSA, 2015
Meat and meat products		–	μg/kg	T	36.9 (0-394) EFSA, 2015
Fish and other seafood		–	μg/kg	T	20.7 (0-169) EFSA, 2015
Milk and dairy products		–	μg/kg	T	1.45 (0-15.2) EFSA, 2015
Ready to eat (including canned dinner)		–	μg/kg	T	5.80 (2.90-8.70) Sakhi et al., 2014
Bottle water		–	μg/L	T	0.20 (0-4.40) EFSA, 2015
Tap water		–	μg/L	P	0

	EFSA, 2015
DEHP concentration in	
	C_{DEHP}
	–
	–
	–
	–
Grains and grain-based products	
	–
	µg/kg
	T
	43 (18-61)
	Sakhi et al., 2014
Fruits and vegetables	
	–
	µg/kg
	T
	4.80 (0.05-9.50)
	Sakhi et al., 2014
Meat and meat products	
	–
	µg/kg
	T
	0 (0-64)
	Sakhi et al., 2014
Fish and other seafood	
	–
	µg/kg
	T
	0 (0-35)
	Sakhi et al., 2014
Milk and dairy products	
	–
	µg/kg
	T
	126 (19-173)
	Sakhi et al., 2014
Ready to eat (including canned dinners)	
	–
	µg/kg
	T
	136 (37-235)
	Sakhi et al., 2014
Bottle water	
	–
	µg/L
	LN
	0.11 ± 0.05
	Santana et al., 2014
Tap water	
	–
	µg/L
	LN
	0.16 ± 0.04
	Santana et al., 2014
Food ration	
	Fr
	–
	–
	–
	–
Grains and grain-based products	
	–
	kg/ration
	U
	0.05-0.07
Dapcich et al., 2004	

Fruits and vegetables	–	
	kg/ration	
	U	
	0.15-0.20	
	Dapcich et al., 2004	
Legumes	–	
	kg/ration	
	U	
	0.06-0.08	
	Dapcich et al., 2004	
Meat and meat products	–	
	kg/ration	
	U	
	0.10-0.13	
	Dapcich et al., 2004	
Fish and other seafood	–	
	kg/ration	
	U	
	0.13-0.15	
	Dapcich et al., 2004	
Milk and dairy products	–	
	kg/ration	
	U	
	0.26-0.34	
	Dapcich et al., 2004	
Ready to eat (including canned dinners)	–	
	kg/ration	
	U	
	0.21-0.41	
	Dapcich et al., 2004	
Food frequency	Ff	
	–	
	–	
	–	
	–	
Grains and grain-based products	–	
	ration/week	
	LN	
	9.60 ± 3.57	
	Present study	
Fruits and vegetables	–	
ration/week		
	LN	
	21.1 ± 7.09	
	Present study	
Legumes	–	
ration/week		
	LN	
	1.80 ± 1.38	
	Present study	
Meat and meat products	–	
ration/week		
	LN	

		5.13 ± 2.81
		Present study
Fish and other seafood		
		–
	ration/week	
		LN
		2.87 ± 1.74
		Present study
Milk and dairy products		
		–
	ration/week	
		LN
		6.86 ± 4.59
		Present study
Ready to eat (including canned dinners)		
		–
	ration/week	
		LN
		3.09 ± 1.82
		Present study
Bottle Water		
		–
		L/day
		LN
		1.40 ± 0.67
		Present study
Tap water		
		–
		L/day
		LN
		1.02 ± 0.50
		Present study
Conversion factor		
		-
		day/week
		-
		7
Bodyweight		
		BW
		kg
		LN
		65.5 ± 14.0
		Present study

Mean, minimum, and maximum values were used for triangular distributions; Mean and standard deviation were used for log-normal; minimum, and maximum values for uniform distributions.
Including canned and non-canned food.
LN= Log-normal; T= Triangular; U= Uniform; P= Punctual

Table 2. Characteristics of the study population from Reus, Tarragona (Spain) (n=45).X**Characteristics of the study population** (n = 45)	**%**		**%**
Maternal age at delivery (years)		*Mother's diet*	
< 20	0	Omnivorous	96
20-29	10	Vegetarians	4
30-39	73	Vegans	0
>40	17	*Water consumption (liters)*	
Twin pregnancy	9	< 1	4
*Maternal pre-pregnancy BMI**		1-2	85
Underweight (<19 kg/m2)	11	>2	11
Normal (19-25 kg/m^2)	52	*Kind of water consumption*	
Overweight (>25 kg/m^2)	26	Tap water	16
Obese (>30 kg/m^2)	11	Bottled water	71
*Maternal pregnancy (20 GW) BMI**		Both	13
Underweight (<19kg/m2)	0	*Eat in a plastic recipient (times/week)*	
Normal (19-25 kg/m^2)	41	Never	69
Overweight (>25 kg/m^2)	44	1-3	4
Obese (>30 kg/m^2)	15	4-6	20
Maternal education		> 6	7
Primary	25	*Eat canned food (times/ week)*	
Secondary	32	Never	18
University	43	1-3	71
Social economic status		4-6	7
High level (> 35000 €/year)	25	> 6	4
Median level (19000-35000 €/year)	57	*Eat Fast-food*	
Low level (< 9000-19000 €/year)	18	Never	29
Maternal country of origin		1 a week	47
Spain	81	>1 a week	24
Other	19	*Eat organic products*	
Marital Status		Never	56
Living with the father	98	Hardly ever	18
Not living with the father	2	Sometimes	20
Maternal smoking		Very often	7
Never smoke	74		
Not during pregnancy	11		
During pregnancy	15		
**BMI= Body mass index*			

925

926**Table 3**. BPA and DEHP total dietary intake in adult populations found in the recent scientific
927literature.

	Year		Total dietary intake (μg/kg bw/day)	Reference
BPA		*		
Belgium	2004	Mean	0.015	Geens et al.,2010
Europe	2006	Mean	1.5	EFSA, 2006
France	2014	Mean range (P50 range; P95 range)	0.038-0.040 (0.033-0.035; 0.077-0.0087)	Bemrah et al.,2014
New Zealand	2004	Mean (P50; P95)	0.008 (0.00; 0.041)	Thomson and Grounds, 2005
Norway	2014	Mean (P50; P95)	0.004 (0.003; 0.01)	Sakhi et al., 2014
Spain	2013	Mean (P95)	0.061 (0.099)	EFSA, 2013 [a]
Spain	2013	Mean (P95)	0.18 (0.33)	EFSA, 2013[b]
Taiwan	2015	Mean (P50;P95)	0.64 (0.27;2.29)	Chen et al., 2016
USA	2010	Mean	0.012	Lorber et al., 2015
Tarragona, Spain	2016	Mean (P5; P95)	0.72 (0.28; 1.41)	Present study
DEHP				
Belgium	2012	Mean	1.59	Sioen et al., 2012
Cambodia	2016	Mean	11.67	Cheng et al., 2013
China	2011-2012	Mean (P97.5)	2.03 (3.64)	Sui et al., 2014
France	2008	Mean	1.46	Martine et al., 2013
Germany	2005	Mean (P50;P95)	2.5 (2.4;4.0)	Fromme et al., 2007
Germany	2005-2006	Mean (P95)	14 (28.5)	Heinemeyer et al., 2013
Norway	2014	Mean	0.42	Sakhi et al., 2014
Switzerland	2009	Mean	1.90	Dickson-Spillmann et al.,2009
USA	2013	Mean	0.67	Schecter et al., 2013
Tarragona, Spain	2016	Mean (P5; P95)	1.00 (0.41; 2.01)	Presentstudy

[a]Only foods specifically codified as canned in the dietary survey are assigned the corresponding occurrence level for BPA. [b]Any food category (at the lowest available level of food category classification) which has been codified as canned in at least one survey is always considered to be consumed as canned in all dietary surveys included in the Comprehensive Database.
* P5, P50, P95 and P97.5 are 5th, 50th, 95th and 97.5th percentile, respectively.

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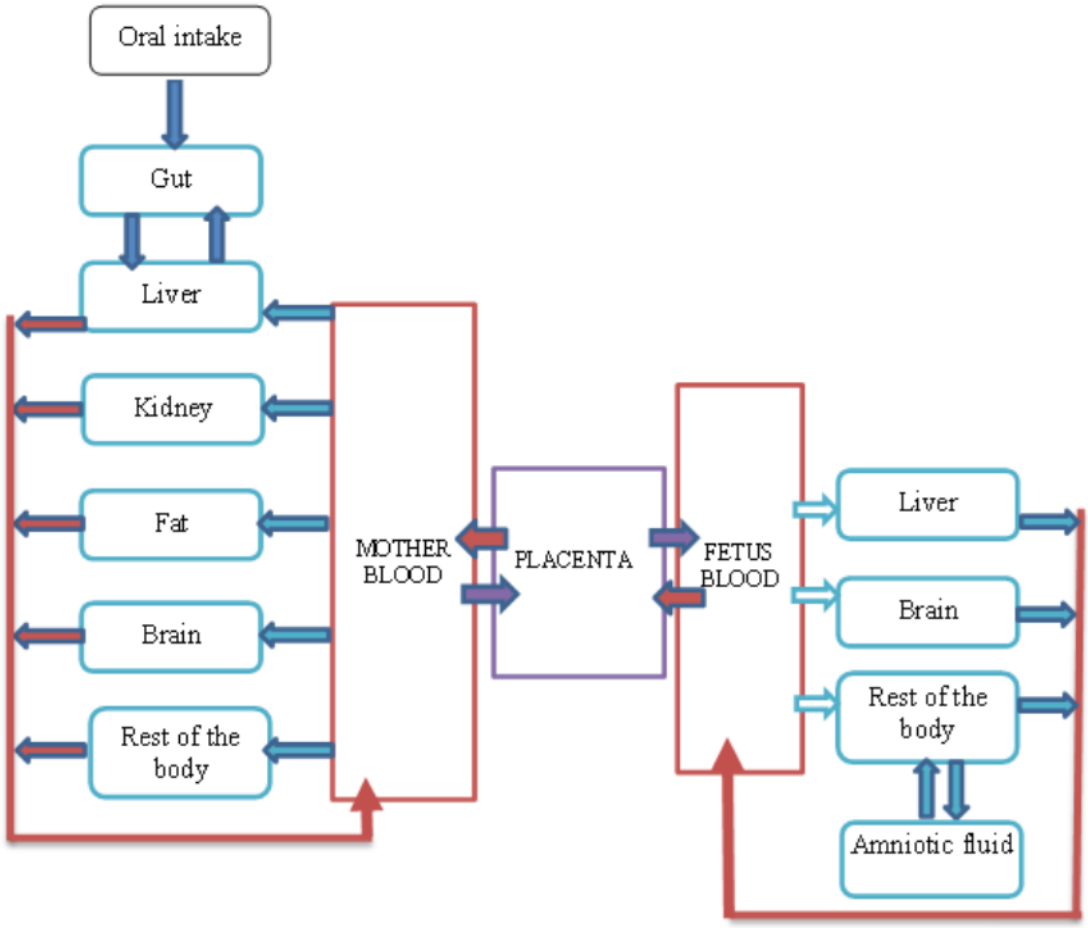

Figure 1. Conceptual structure of pregnancy PBPK model for BPA and DEHP. Adapted PBPK model for pregnant women and fetus which included the body organs compartments for both. The compartments like placenta and fetus compartments were considered as a sub-model in order to predict the internal dosimetry for the fetus.

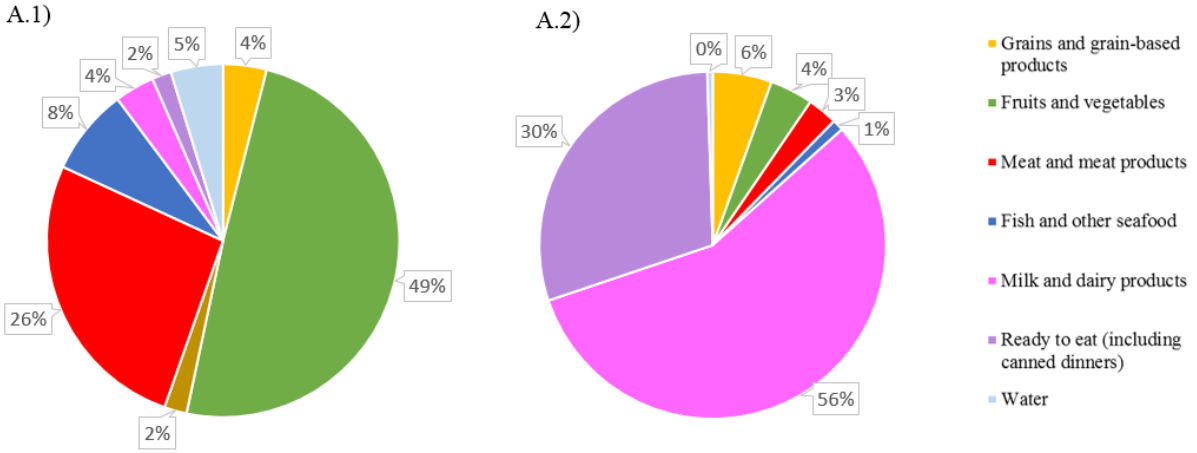

Figure 2. Food categories contribution to the total dietary intake of BPA (A.1) and DEHP (A.2) in µg/kg bw/day. Results are given in mean (5th percentile; 95thpercentile).

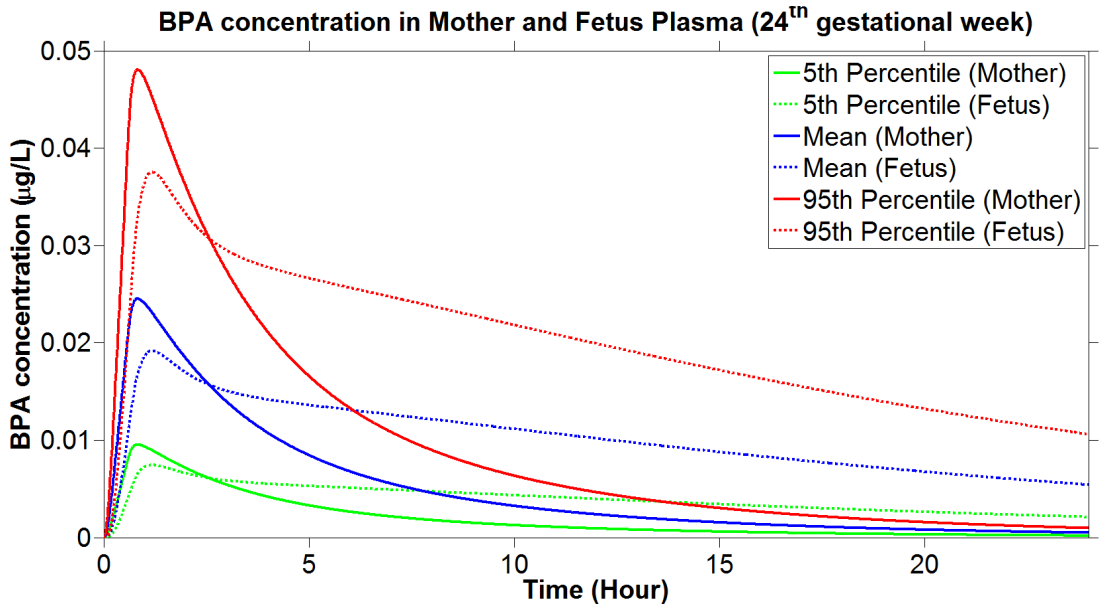

Figure 3. Time versus BPA plasma concentration for mothers and fetuses, considering different exposure scenarios (5th percentile; mean; 95th percentile) and only one food intake dose.

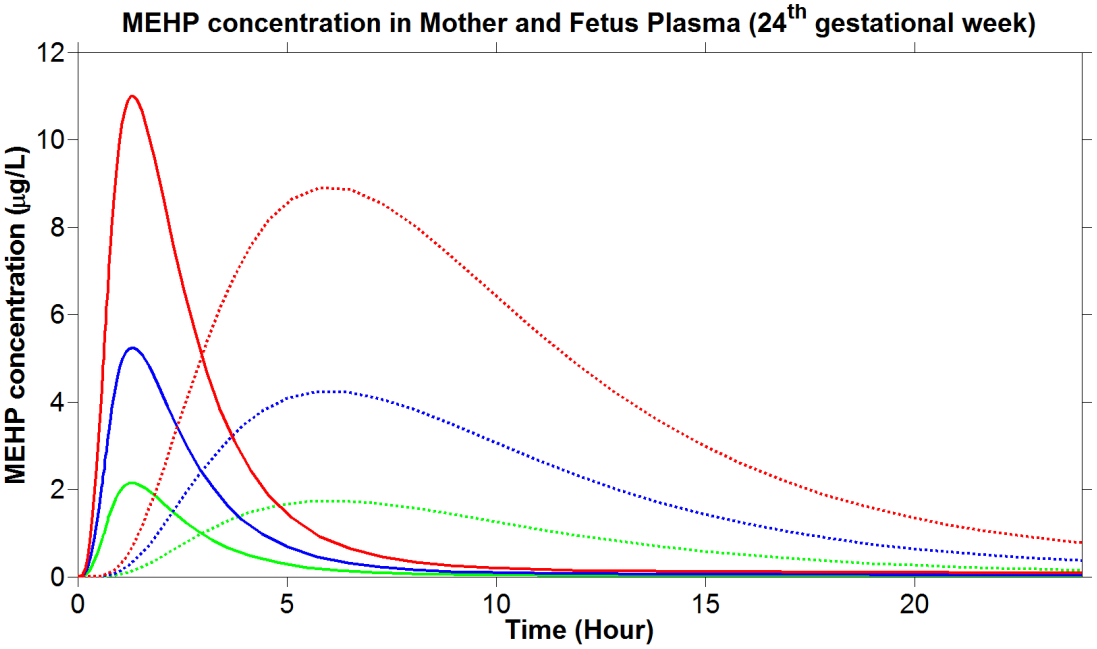

Figure 4. Time versus MEHP plasma concentration for mothers and fetuses, considering different exposure scenarios (5th percentile; median; 95th percentile) and only one food intake dose.

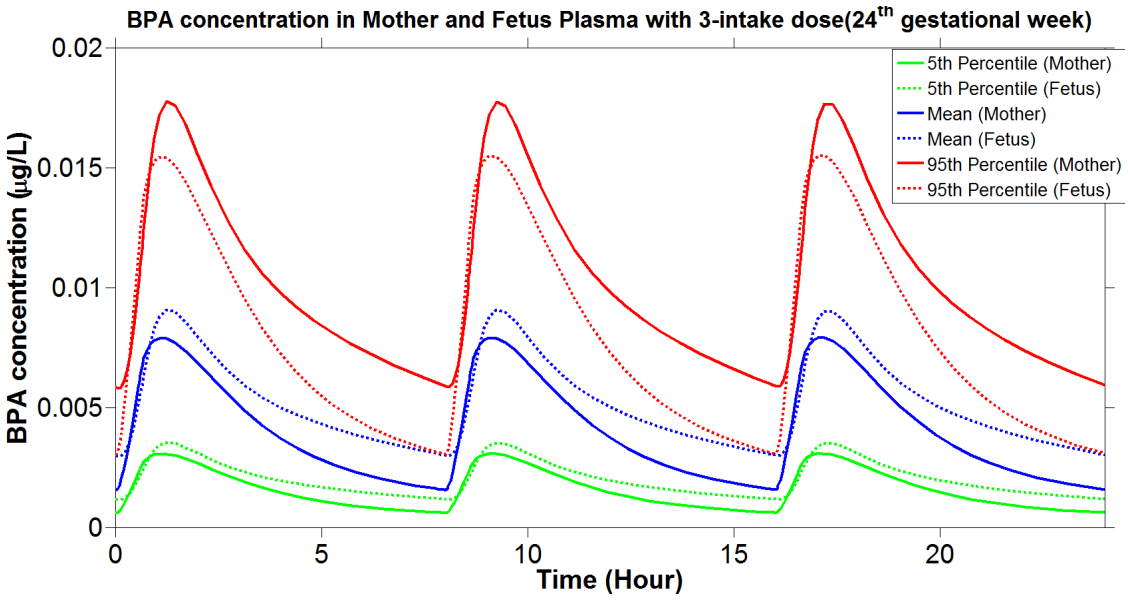

Figure 5. Time versus BPA plasma concentration for mothers and fetuses, considering different exposure scenarios (5th percentile; mean; 95th percentile) and three-food intake dose.